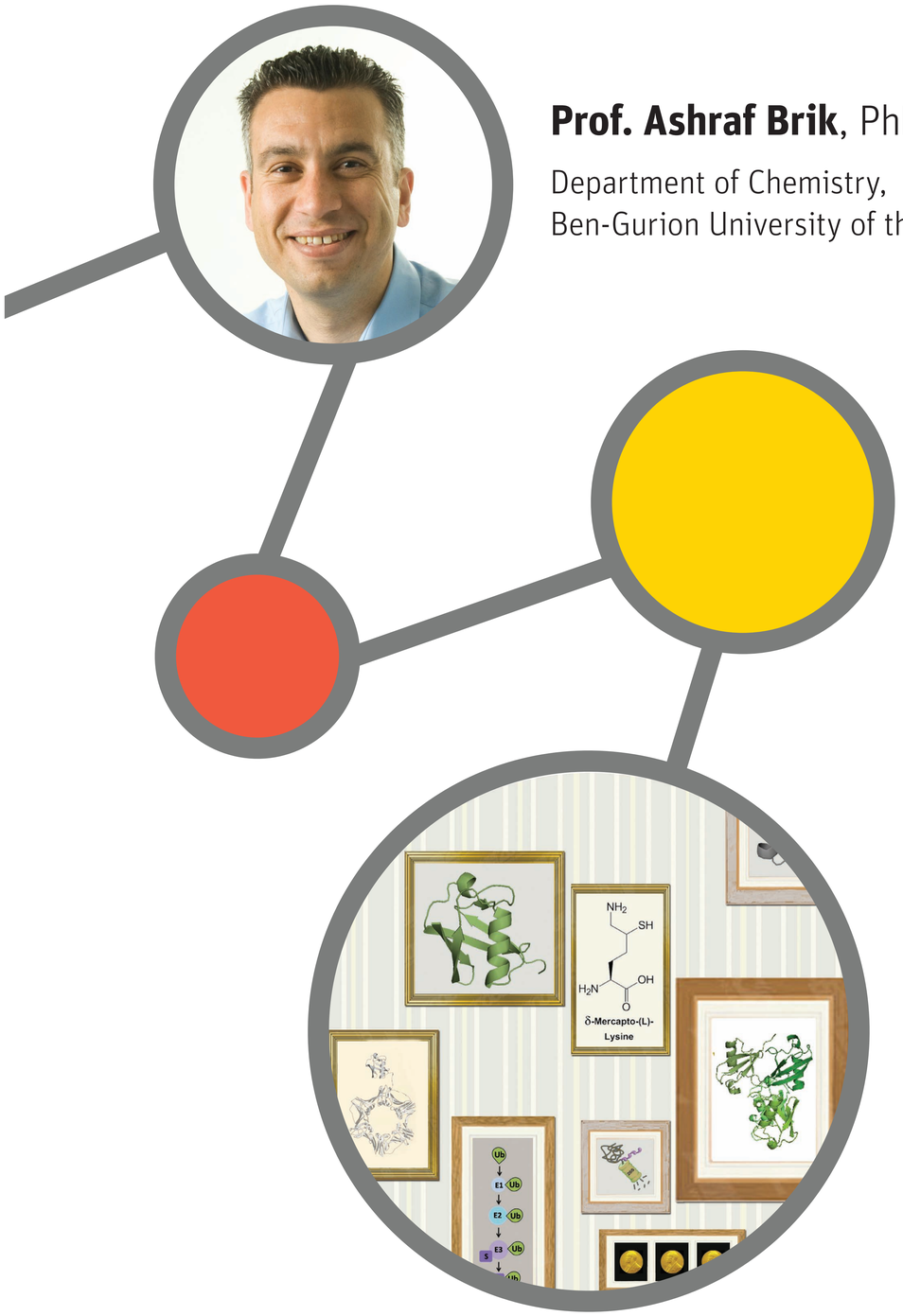

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פרס טבע למצוינות
על שם אלי הורביץ

Research accomplishments

The Brik research laboratory has been developing novel chemical biology approaches to shed light, at the molecular level, on fundamental questions as to the role of posttranslational modifications on the protein structure and function. One such example is ubiquitination—the attachment of a ubiquitin protein to a protein target, affecting a variety of biological processes. Not surprisingly, the ubiquitin signal plays a key role in various diseases, such as neurological disorders, infectious diseases and cancer. Hence better understanding of this signal is crucial for combating various diseases.

In ubiquitination, three enzymes, E1-E3, collaborate to link the C-terminal Gly of ubiquitin to the Lys side chain of the protein target through an isopeptide bond. Conjugation of the ubiquitin molecule to a protein target may involve an ubiquitin monomer or a chain of ubiquitins of various lengths and linkage types.

The evolving complexity of the ubiquitin signal and the recent discoveries of its involvement in a wide range of biological functions continue to dazzle scientists in many ways and hence engage several research groups aiming to decipher the molecular bases of this signal and its importance in health and diseases. Yet, research in this field, including structural and functional analyses, the development of reagents and understanding the enzymatic machineries and the factors involved in this signal, has been challenged by the inability to obtain homogenous ubiquitin bioconjugates at a workable level from cells, and even from cell free reconstituted enzymatic systems where conjugation often proceeds in an uncontrolled manner.

The Brik research group has reported a number of novel chemical methods that offer solutions to these challenges and prepare any ubiquitin conjugate in high homogeneity, purity and large quantities in order to shed light on various processes related to the ubiquitin signal. To that effect, the group reported a highly efficient and site-specific peptide and protein ubiquitination emulating the action of the enzymatic machinery. This battery of chemical tools allowed for the first semisynthesis of homogeneously ubiquitinated alpha-synuclein and other proteins to support the ongoing efforts aiming at studying the effect of ubiquitination in health and disease.

Additionally, the group achieved the total chemical synthesis of all di-ubiquitin chains as well as the tetra-ubiquitin chains to shed light on how these chains achieve their function. The group also expanded these approaches to target different deubiquitinases in the ubiquitin system to shed light on their role in health and disease, and ultimately, for drug development. As a result, great opportunities have become now available for chemical biologists, biochemists and biologists to study the ubiquitin signal at the molecular level to reveal unknown aspects of this amazing and diverse signal.